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Health and Environmental Effects Profile for Malononitrile

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR MALONONITRILE

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16. ABSTRACT

The Health and Environmental Effects Profile for Malononitrile was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Malononitrile has been determined to be a systemic toxicant. A Reference Dose (RfD), defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effect during a lifetime, for malononitrile is 0.02 µg/kg/day for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for malononitrile is 100.

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This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1985.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic exposures. An RfD is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, RfDs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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EXECUTIVE SUMMARY

Malononitrile is a colorless solid at ambient temperature. It is soluble in water and in a number of organic solvents (Windholz, 1983). As of January, 1985, one chemical company manufactured or imported this chemical in the United States (SRI, 1985). The U.S. production/importation volume data for malononitrile are not available. Malononitrile is used as an intermediate for the synthesis of organic chemicals and as a leaching agent for gold (Hawley, 1981).

Pertinent data specifically regarding the fate and transport of malononitrile in air, water or soil could not be located in the available literature as cited in the Appendix. From the limited data available, it has been speculated that biodegradation and volatilization of malononitrile from surface water and soil, and hydrolysis in water and soil may not be significant. More data on biodegradation potential are needed to assess the environmental persistence of this compound.

Data on the level of malononitrile in air, drinking water and food could not be located in the available literature as cited in the Appendix.

The information concerning aquatic toxicity of malononitrile consists of LC_{50} values for two freshwater and one saltwater fish species. All three species -- rainbow trout, mosquitofish and mummichog -- had similar LC_{50} values. The lowest reported acutely toxic concentration was 1.63 mg/ℓ, the 96-hour LC_{50} for rainbow trout (Abram and Wilson, 1979).

After oral administration to rats, malononitrile was readily absorbed from the gastrointestinal tract and liberated cyanide into the tissues (Ahmed and Farooqui, 1982). Additional studies by Panov (1969, 1970) have shown that malononitrile exerts systemic effects after inhalation, oral, ocular or dermal exposure, and is therefore also absorbed by these routes.

Cyanide levels after malononitrile administration accumulated primarily in the liver, secondarily in the kidney and to a lesser degree in the CNS (Ahmed and Farooqui, 1982).

After malononitrile administration, thiocyanate is the main urinary excretion product (Frankenberg and Sorbo, 1973); thiocyanate is formed by the reaction of cyanide with thiosulfate, which is catalyzed by the enzyme rhodanese. Thiocyanate is excreted in the urine. At least 78.9% of an intraperitoneally administered dose of malononitrile was excreted as thiocyanate in the urine of mice (Frankenberg and Sorbo, 1973). In vitro toxicity and metabolism studies indicated that cyanide was released gradually from malononitrile (Stern et al., 1952). In vivo pretreatment of mice with CCl_4, which impairs the mixed function oxidase system, resulted in decreased liberation of cyanide in mice treated with malononitrile and in isolated microsomal preparations treated with malononitrile in vitro, indicating that microsomal enzymes catalyze the release of cyanide from malononitrile (Willhite and Smith, 1981).

Pertinent data regarding the carcinogenicity or reproductive effects of malononitrile could not be located in the available literature as cited in the Appendix. Only one study was available on the mutagenicity of malononitrile; the authors reported that the compound did not induce reverse mutations in S. typhimurium TA100 (Rietveld et al., 1983).

Panov et al. (1972) administered, by gastric intubation, 0, 0.25 or 0.50 mg/kg/day malononitrile to male Wistar rats 6 days/week for 120 days. Rats were sacrificed for examination of tissue pathology 2 months after the final treatment. Administration of the compound did not affect mortality rates.

Fluctuating levels of histamine, histaminase, cholinesterase, coproporphyrins and 5-hydroxyindoleacetic acid were attributed to malononitrile administration. Dose-related increased severity of lesions was observed in the liver and spleen. In the liver, congestion became more pronounced with dose, and degeneration and necrosis occurred at 0.50 mg/kg/day. In the spleen, hemosiderosis and reticulocytosis were observed at 0.25 mg/kg/day and decreased hematopoiesis occurred at 0.50 mg/kg/day. The gastrointestinal tracts of the treated rats were marked by edema and signs of inflammation.

Inhalation exposure of rats to 0.036 mg/ℓ malononitrile vapor for 2 hours/day for 35 days led to signs of irritation during treatment (Panov, 1970). Treated rats showed a slight tendency toward reticulocytosis and, on days 22 and 35, had decreased hemoglobin concentrations, relative to controls. The weight of the lungs, but not the kidney, liver or brain, was increased. Krysiak et al. (1976) gave groups of male Wistar rats 0, 2 or 10 mg/kg/day, and females 0, 2, 10 or 15 mg/kg/day malononitrile by intraperitoneal injection for 6 weeks. For males, dose-related increases in blood urea concentration and liver and adrenal weight were observed. In females, reticulocytosis, erythrocytopenia, increased glucose concentrations and increases in liver and spleen weights were dose-related.

Early clinical use of intravenous doses of malononitrile in psychiatric patients (MacKinnon et al., 1949; Hyden and Hartelius, 1948) was found to be of little or no therapeutic benefit; however, toxic reactions included flushing, tachycardia, headaches, chills and nausea. Acute oral LD_{50}s in rats and mice have ranged from 14-119 mg/kg (Ahmed and Farooqui, 1982; Tanii and Hashimoto, 1985; Krysiak et al., 1976; Panov et al., 1972), and most toxic effects after acute exposure are the same as those seen after cyanide

exposure. Szabo et al. (1982), however, observed that high doses of malononitrile exerted neither an ulcerogenic nor an adrenocorticolytic effect, unlike other nitriles. In rats and rabbits given malononitrile parenterally, CNS effects including deposition of polynucleotide and protein substances and necrosis of myelin tissue, were described by Hydin and Hartelius (1948) and Hicks (1950).

A provisional RfD of 0.02 µg/kg/day or 1.5 µg/day for a 70 kg human was derived from the rat subchronic oral LOAEL of 0.25 mg/kg/day, 6 days/week for 120 days in the study by Panov et al. (1972). An uncertainty factor of 10,000 was used. The LOAEL was associated with congestion of the liver and hemosiderosis and reticulocytosis in the spleen. An RQ of 100 was derived based on the liver necrosis and reduced hematopoiesis in the spleen observed at 0.50 mg/kg/day, 6 days/week in the 120-day oral study by Panov et al. (1972). Because pertinent data regarding the carcinogenicity of malononitrile were not located, the chemical, based on U.S. EPA (1984) guidelines, was classified as CAG Group D, meaning malononitrile cannot be classified as a human carcinogen.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
CAS	Chemical Abstract Service
CNS	Central nervous system
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
RNA	Ribonucleic acid
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TWA	Time weighted average
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

The chemical commonly known as malononitrile is also known as propanedinitrile, methylene cyanide, dicyanomethane and cyanoacetonitrile (Windholz, 1983). The structure, empirical formula, molecular weight and CAS Registry number for this chemical are as follows:

$$N\equiv C-CH_2-C\equiv N$$

Empirical formula: $C_3H_2N_2$

Molecular weight: 66.06

CAS Registry number: 109-77-3

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Malononitrile is a colorless solid at ambient temperatures. It is soluble in water, acetone or benzene, and is very soluble in ethanol and ethyl ether (Windholz, 1983). Some of the physical properties of this compound are listed below.

Melting point:	32°C	Windholz, 1983
Boiling point: at 1 atm	218-219°C	Windholz, 1983
Density, 20/4°C:	1.1910 g/cm³	Windholz, 1983
Flash point: (closed cup)	112°C	Aldrich, 1986

The two most well-known chemical reactions of nitriles are hydrolysis to the corresponding acid and reduction to the corresponding primary amine (Gutsche and Pasto, 1975); however, these reactions do not occur under environmental conditions. The hydrolysis of malononitrole in dilute aqueous alkaline solution was reported by Block et al (1973). One of the two cyano groups underwent 95% hydrolysis in 15 hours with the formation of ammonia and $CNCH_2COOH$; no $CH_2(COOH)_2$ was formed.

1.3. PRODUCTION DATA

The U.S. EPA TSCA Inventory (U.S. EPA, 1977) listed four companies as producers/importers of malononitrile in the United States in 1977. As of January, 1985, Dynamit Nobel of America Inc., Stony Point, NY, was the only producer/importer of this chemical in the United States (SRI, 1985). More recent production or importation data for malononitrile are not available. Malononitrile can be produced from ClCN, CH_3CN and HCN at 700°C (Jenks, 1979).

1.4. USE DATA

Malononitrile is used for organic synthesis and as a leaching agent for gold (Hawley, 1981). One of the important commercial uses of malononitrile is in the production of o-chlorobenzalmalononitrile, a military and riot control chemical agent (CS), which is a good tear gas. It is also used in the synthesis of vitamin B_1, plastics and agricultural chemical products (Hoecker et al., 1977).

1.5. SUMMARY

Malononitrile is a colorless solid at ambient temperature. It is soluble in water and in a number of organic solvents (Windholz, 1983). As of January, 1985, one chemical company manufactured or imported this chemical in the United States (SRI, 1985). The U.S. production/importation volume data for malononitrile are not available. Malononitrile is used as an intermediate for the synthesis of organic chemicals and as a leaching agent for gold (Hawley, 1981).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

One important source by which malononitrile enters the environment is its formation as a hydrolysis product of o-chlorobenzalmalononitrile, a riot control agent (Verschueren, 1983). Other likely environmental sources of malononitrile include its production and user sites. Pertinent data regarding the fate and transport of malononitrile in any environmental medium could not be located in the available literature as cited in the Appendix. Even values for basic physical properties like vapor pressure and K_{ow}, necessary to predict its environmental behavior, were not located in the available literature. One study (Marion and Malaney, 1963) reported that malononitrile was inhibitory to Alcaligenes faecalis, a bacterial species found in activated sludge flora that degraded several nitriles. Since malononitrile is structurally similar to acetonitrile and since biodegradation and volatilization are important in the loss of acetonitrile from soil and water, the loss of malononitrile through volatilization should be evaluated (U.S. EPA, 1985a). The vapor pressure of malononitrile at 20°C was estimated from the method suggested by Lyman et al. (1982) to be 0.089 mm Hg. Since malononitrile is soluble in water, and the vapor pressure at 20°C is not high (vapor pressure of acetonitrile at 20°C is 74 mm Hg) (U.S. EPA, 1985a), volatilization from soil and water may not be significant. The UV and visible absorption spectrum of an aqueous solution of malononitrile was studied by Mendelson et al. (1954). A freshly prepared solution of malononitrile did not show any peaks either in the UV or visible regions; however, when these solutions were allowed to stand at room temperature for up to 105 days, two peaks at 268 and 358 nm were observed. Although no specific reason for the appearance of the peaks was provided, they were

speculated to be due to an unspecified chemical reaction of malononitrile in water. Unless more information becomes available, it is not possible to predict the nature of this chemical reaction. Without more data on the biodegradability and hydrolysis of this compound, no conclusion about its environmental persistence can be made.

2.2. SUMMARY

Pertinent data specifically regarding the fate and transport of malononitrile in air, water or soil could not be located in the available literature as cited in the Appendix. From the limited data available, it has been speculated that volatilization of malononitrile from surface water and soil may not be significant. More data on hydrolysis and biodegradation potential are needed to assess the environmental persistence of this compound.

3. EXPOSURE

Pertinent data regarding the level of malononitrile in air, drinking water and food could not be located in the available literature as cited in the Appendix.

4. PHAPMACOKINETICS

4.1. ABSORPTION

Malononitrile and its metabolites has been found to be readily absorbed after oral administration (Panov et al., 1972; Ahmed and Farooqui, 1982). Ahmed and Farooqui (1982) administered 60 mg/kg of malononitrile orally to six male Sprague-Dawley rats and killed all animals 1 hour later. Samples of whole blood, liver, kidney, brain and gastric contents were collected and analyzed for cyanide concentrations. At sacrifice, the levels of cyanide in the liver, kidney and brain were 3890, 1012 and 649 µg/g tissue, which was comparable with levels measured after dosing with potassium cyanide. The cyanide level in the blood was also comparable following dosing with malononitrile or potassium cyanide. The amount of malononitrile or cyanide in the gastric contents was not reported.

Panov (1969, 1970) studied the toxicity of malononitrile after inhalation, oral, ocular and dermal application. After repeated inhalation exposure, 10 white rats displayed decreases in hemoglobin level, reticulocytosis and fluctuations in body temperature (Section 5.5.). Single oral doses in mice led to tissue hyperemia and "dystrophy" of intracellular fats and proteins. Ocular and dermal applications led to convulsions and respiratory impairment in rabbits and systemic cyanosis in mice, respectively. These results suggest that absorption of malononitrile occurs by all of these routes of administration.

4.2. DISTRIBUTION

After oral exposure, malononitrile rapidly yields cyanide, which is distributed to tissues. As discussed in Section 4.1., cyanide levels in the brain, liver and kidney of rats 1 hour after oral administration of malononitrile were comparable with those observed after potassium cyanide administration, suggesting that only one cyanide was released (Ahmed and Farooqui,

1982). Accumulation of cyanide in the liver was ~4 times that of the kidney and 6 times that of the brain. Brain levels of cyanide immediately after oral administration of 356.4 mg/kg malononitrile in ddY mice were 0.74 μg/g tissue (Tanii and Hashimoto, 1985).

4.3. METABOLISM

As indicated in Section 4.2., malononitrile is metabolized to cyanide. After intraperitoneal administration of 7.3 mg/kg malononitrile in C57 black mice, blood levels of cyanide peaked at 8-16 minutes postinjection and remained at greater than half the peak value at 30 minutes (Frankenberg and Sorbo, 1973).

Stern et al. (1952) studied the *in vitro* toxicity of malononitrile and concluded that cyanide is released gradually. The rate of respiration in malonitrile-treated tissue slices of brain, liver and kidney from rats and guinea pigs was measured by manometric techniques. A concentration of 0.01 M malononitrile inhibited respiration progressively with time; inhibition of respiration by potassium cyanide was not progressive.

One detoxication pathway of cyanide is the conversion to thiocyanate, a reaction catalyzed by the enzyme rhodanese; thiosulfate is an effective thio donor. When malononitrile and sodium thiosulfate were added to homogenates of rat liver, kidney or brain, the formation of thiocyanate increased linearly with time (Stern et al., 1952). The rate of thiocyanate formation was greatest in liver, followed by the kidney and brain and corresponded to the relative rhodanese activities in these tissues. When malononitrile was incubated with thiosulfate and purified rhodanese, thiocyanate was not formed, indicating that malononitrile did not release cyanide spontaneously, but that other enzymes present in the tissue homogenate were necessary.

The effects of mixed function oxidase inhibitor (CCl_4) pretreatment on tissue cyanide levels after malononitrile administration were studied by Willhite and Smith (1981) and Tanii and Hashimoto (1985). Willhite and Smith (1981) gave a subcutaneous dose of 20% CCl_4 in vegetable oil 24 hours before an intraperitoneal dose of 18 mg/kg malononitrile to male CD-1 mice. The mice were sacrificed 2.5 hours after the second injection for analyses of brain and liver cyanide levels. Compared with a group of mice that were not pretreated, the CCl_4-treated mice had negligible cyanide levels in these two organs. This result suggests that release of cyanide was catalyzed by microsomal enzymes. In vitro studies using a liver microsomal preparation from mice pretreated intraperitoneally with CCl_4 revealed an ~35-fold decrease in cyanide formation (Willhite and Smith, 1981).

Tanii and Hashimoto (1985) pretreated ddY mice intraperitoneally with 20% CCl_4 in olive oil. Twenty-four hours later, the mice were dosed orally with 3 times the LD_{50} (~323 mg/kg) of malononitrile, and their brains were removed. Unlike the previous results, CCl_4 pretreatment negligibly decreased brain cyanide concentration and did not prevent death of the treated mice. The differences between these results and those of Willhite and Smith (1981) may be attributed to the route of administration and doses used.

4.4. EXCRETION

Frankenberg and Sorbo (1973) intraperitoneally administered 110 µmol/kg (~7.3 mg/kg) malononitrile to 12 male C57 black mice. The mice were then placed in metabolism cages, urine was collected for 2-24 hours, and thiocyanate concentration was then assessed colorimetrically. Two days before treatment, thiocyanate excretion was 25.4 and 22.8 µmol/kg bw,

respectively; values measured 2 days after administration were 102 (day 1) and 33 (day 2) µmol/kg. The yield, expressed as a percentage of the dose of compound administered, was 78.9%.

4.5. SUMMARY

After oral administration to rats, malononitrile was readily absorbed from the gastrointestinal tract and liberated cyanide into the tissues (Ahmed and Farooqui, 1982). Additional studies by Panov (1969, 1970) have shown that malononitrile exerts systemic effects after inhalation, oral, ocular or dermal exposure, and is therefore also absorbed by these routes. Cyanide levels after malononitrile administration accumulated primarily in the liver, secondarily in the kidney and to a lesser degree in the CNS (Ahmed and Farooqui, 1982).

After malononitrile administration, thiocyanate is the main urinary excretion product (Frankenberg and Sorbo, 1973); thiocyanate is formed by the reaction of cyanide with thiosulfate, which is catalyzed by the enzyme rhodanese. Thiocyanate is excreted in the urine. At least 78.9% of an intraperitoneally administered dose of malononitrile was excreted as thiocyanate in the urine of mice (Frankenberg and Sorbo, 1973). *In vitro* toxicity and metabolism studies indicated that cyanide was released gradually from malononitrile (Stern et al., 1952). *In vivo* pretreatment of mice with CCl_4, which impairs the mixed function oxidase system, resulted in decreased liberation of cyanide in mice treated with malononitrile and in isolated microsomal preparations treated with malononitrile *in vitro*, indicating that microsomal enzymes catalyze the release of cyanide from malononitrile (Willhite and Smith, 1981).

5. EFFECTS

5.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of malononitrile in animals or humans could not be located in the available literature as cited in the Appendix. This compound has not been scheduled for testing by the National Toxicology Program (NTP, 1986).

5.2. MUTAGENICITY

Rietvald et al. (1983) assayed malononitrile for the induction of reverse mutations in Salmonella typhimurium strain TA100, without metabolic activation. The compound was dissolved in 0.1 mL DMSO, and concentrations ranging from 0-2000 µg/plate were used in the plate incorporation assay. Under the conditions of this assay, malononitrile was not genotoxic (data not reported).

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of malononitrile could not be located in the available literature as cited in the Appendix.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding the other reproductive effects of malononitrile could not be located in the available literature as cited in the Appendix.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Pertinent data regarding the chronic toxicity of malononitrile could not be located in the available literature as cited in the Appendix. In the only available study concerning subchronic oral exposure to malononitrile (Panov et al., 1972), seven male Wistar rats/group were given 0.25 or 0.50 mg/kg/day by gastric intubation, 6 days/week for 120 days. The compound was administered in water. A separate control group of eight rats received intubation with water only. Before the initiation of the experimental

period and 4 times throughout treatment, blood samples were taken to measure histamine, histaminase and total cholinesterase. Urine samples were collected once before study initiation and 3 times during testing from groups of two or three rats. These samples were analyzed for coproporphyrins and 5-hydroxyindoleacetic acid levels. Upon sacrifice, 2 months after the end of treatment, the liver, spleen, intestine, tongue, stomach, small intestine and brain of some rats (five at 0.25 mg/kg, four at 0.50 mg/kg and three controls) were assayed for -SH groups, S-S groups and soluble proteins. Pathological examinations of the liver, spleen, stomach and small intestine were also performed. Formalin sections of these tissues were stained for analysis of connective tissue collagen, acid mucopolysaccharides, neutral mucopolysaccharides and RNA.

Panov et al. (1972) found greatly fluctuating, but generally increased, body weight in the treated groups. Levels of histamine and histaminase activities over time fluctuating in opposite directions were indicative of inhibition of histaminase activity. At ~120 days, there was a marked rise in blood cholinesterase in both treated groups, followed by a rapid decrease after treatment ceased. The biological significance of this finding is unclear. Urinary coproporphyrins were elevated in a dose-related manner after 80 days of treatment, but were below control values after 120 days. The authors attributed the 80-day peaks to impaired liver function. Urinary 5-hydroxyindoleacetic acid levels followed a similar course, although less pronounced.

In most organs tested there were dose-related decreases in -SH group levels and increases in S-S levels at sacrifice. These trends were most pronounced in the liver, spleen and brain. Soluble protein concentrations were lower in all organs in a dose-related manner.

At 0.25 mg/kg/day, the hepatocytes exhibited albuminoid degeneration, and there was pronounced congestion in both the centrilobular and venous portal regions. Sections were characterized by depletion of RNA and glycogen. At 0.50 mg/kg, there was significant congestion, with degeneration and focal hepatocellular necrosis. At 0.25 mg/kg, the spleens had a number of hemolyzed red cells and reticulocytes, as well as hemosiderin filled cells. At the higher dose, the spleens were markedly congested, and the red pulp lacked red or white cells, but had multinucleated reticular cells. The white pulp remained intact. The stomach and intestinal mucosa of rats from both treated groups were characterized by edema, lymphoid infiltration, changes in RNA content (generally increased at 0.25 mg/kg but decreased at 0.50 mg/kg) and inflammation. Results of histological examination of control rats were not reported. There was no treatment-related increase in mortality in either dose group.

An inhalation study was conducted by Panov (1970) in which 10 white rats of unspecified sex and strain (initial mean weight, 276.5 g) were exposed to 0.036 mg/l of malononitrile vapor 2 hours/day for 35 days. Ten rats (initial mean weight, 273.5 g) served as controls. At various times throughout the experiment, the parameters assessed were body weight, rectal temperature, hematological measures, summation thresholds, hippuric acid excretion and oxygen consumption in vivo. Seven days after the final exposure session, the rats were sacrificed and selected organs were removed and weighed, and oxygen consumption was measured in lung homogenates.

During exposure, treated animals acted agitated, and frequently sniffed, rubbed their faces and showed signs of accelerated respiration. There were no differences between controls and treated rats in body weights, erythrocytes, leukocytes, summation thresholds or oxygen consumption during treatment, or in in vitro oxygen consumption in lung homogenates after treatment.

Panov (1970) observed a fluctuating hyperthermia in the treated group between days 19 and 35 of exposure. A not statistically significant ($p>0.05$) trend toward reticulocytosis in the treated animals was recorded throughout the study. On days 22 and 35, exposed rats had decreased hemoglobin concentration ($p<0.001$). An apparent decrease in hippuric acid outflow was explained by a reduced urinary excretion rate in treated rats. Lung weight was significantly increased after exposure, relative to controls, although the weights of the liver, kidneys and brain were unaffected.

Subacute intoxication with intraperitoneal administration of malononitrile was studied by Krysiak et al. (1976). In the first of two experiments, a total of 30 male Wistar rats weighing 120-250 g were injected daily with 2 or 10 mg/kg of malononitrile for 6 weeks. In the second experiment, a total of 36 female rats of the same weight were given intraperitoneal doses of 2, 10 or 15 mg/kg/day. Both experiments used control rats, although the exact numbers were unclear. After the 6-week treatment period, hematological parameters (hemoglobin concentration, erythrocyte, total leukocyte, neutrophil, lymphocyte, platelet and reticulocyte counts), blood biochemistries (glucose, urea and protein concentrations, and alkaline phosphatase units) and hepatic tests (number of thymol and zinc units) were assayed. Upon sacrifice shortly after the end of treatment, the relative weights of the liver, kidneys, spleen, lungs, adrenals and heart were measured.

In males exposed to 2 mg/kg, there were statistically significant (by t-test analysis) increases in reticulocytes, blood urea concentration and relative spleen weights, compared with controls. At 10 mg/kg, males had significantly decreased numbers of neutrophils, increased urea concentration and relative adrenal and liver weight. Females given 2 mg/kg/day had a

statistically significant decreased percentage of lymphocytes and increased kidney weights; all other observed parameters appeared normal. At 10 mg/kg/day, females had reticulocytosis, increased blood urea concentration and significantly elevated relative weights of the kidney, spleen, adrenals and heart. Females treated with 15 mg/kg/day had significantly decreased erythrocyte and platelet counts, reticulocytosis, increased blood glucose and urea concentration and decreased hepatic thymol and zinc units. These rats also had significantly increased relative weights of liver, spleen and adrenals. For the males, the only clearly dose-related effects were elevations in blood urea concentration and relative liver and adrenal weights. Reticulocytosis, erythrocytopenia, increased glucose concentrations, and increased liver and spleen weights were dose-related in females. SGOT and SGPT levels were not affected by treatment.

5.6. OTHER RELEVANT INFORMATION

Intravenous administration of malononitrile has been used in psychiatry for treating schizophrenic and manic-depressive patients (Mackinnon et al., 1949; Hyden and Hastelius, 1948); however, its use has been determined to have little or no therapeutic benefit.

In both of these studies (Mackinnon et al., 1949; Hyden and Hartelius, 1948), the treated patients showed a consistent series of reactions in response to the injection. These reactions included facial flushing, tachycardia, feelings of discomfort, mild headache and chills. Nausea, vomiting, slight muscular spasms and dysphoria were occasionally observed. Toxic symptomatology could be reversed by the administration of sodium thiosulfate. Primarily because of these toxic effects, the use of malononitrile in psychiatric medicine was discontinued.

Single dose LD_{50}s for malononitrile in rats and mice have ranged from 14-119 mg/kg (Ahmed and Farooqui, 1982; Tanii and Hashimoto, 1985; Sax, 1985; Krysiak et al., 1976; Panov et al., 1972) after oral administration and 14.5-20.6 mg/kg (Frankenberg and Sorbo, 1973; Jones and Israel, 1970; Krysiak et al., 1976; Willhite and Smith, 1981) after intraperitoneal dosing. Signs and symptoms after acute poisoning are the same as those seen after cyanide administration; they include respiratory difficulties, anoxic convulsions, headaches, incoordination, nausea and cyanosis (Ahmed and Farooqui, 1982; Frankenberg and Sorbo, 1973; NIOSH, 1978; Szabo et al., 1982; Jones and Israel, 1970). Rapid recovery is usually seen after thiosulfate administration (Jones and Israel, 1970; Willhite and Smith, 1981). Szabo et al. (1982) administered a total oral dose of 2.7 mmol/kg (~178 mg/kg) malononitrile over 4-5 days to female Sprague-Dawley rats and found that, unlike other nitriles, it exerted neither an ulcerogenic nor an adrenocorticolytic effect. NIOSH (1978) stated that, although all nitriles appear to exert toxicity by the liberation of cyanide, there are substantial differences in the dose amounts and time intervals necessary to induce toxicity.

Acute CNS toxicity from malononitrile administered to rabbits and rats has been studied by Hyden and Hartelius (1948) and Hicks (1950). Hyden and Hartelius (1948) injected rabbits intravenously with a single dose of 4-6 mg/kg malononitrile and sacrificed them at various times postinjection. Nervous tissue was fixed according to a freeze-drying method. An unspecified analytical technique revealed increases in the polynucleotide and protein substances in the anterior horn cells, in sensory and motor spiral cells and in the cerebral cortical ganglion cells. Study of the ganglion cells in rabbits injected repeatedly for 3-488 days revealed the same

effects. Hicks (1950) administered repeated 5 mg/kg intraperitoneal doses of malononitrile to white rats in an attempt to cause maximum brain damage without lethality. The rats were sacrificed between 24 and >48 hours after the injections. Within the nervous system, necrosis of the myelin layers of the white matter, particularly in the corpus striatum, was observed. Damage was also found in the thyroid acinar cells and the parathyroid, with minimal lesions in the ventricular myocardium.

In liver, kidney and brain homogenates from Sprague-Dawley rats treated orally with malononitrile at 60 mg/kg, the compound induced a significant decline in cytochrome c oxidase activity (Ahmed and Farooqui, 1982). These results were not replicated in in vitro test systems (Ahmed and Farooqui, 1982; Willhite and Smith, 1981). Based upon empirical second-order rate constants, Castro et al. (1978) characterized malononitrile as a slow reductant in the oxidation of oxyhemoglobin.

5.7. SUMMARY

Pertinent data regarding the carcinogenicity or reproductive effects of malononitrile could not be located in the available literature as cited in the Appendix. The compound did not induce reverse mutations in S. typhimurium TA100 (Rietveld et al., 1983).

Panov et al. (1972) administered, by gastric intubation, 0, 0.25 or 0.50 mg/kg/day malononitrile to male Wistar rats 6 days/week for 120 days. Rats were sacrificed for examination of tissue pathology 2 months after the final treatment. Administration of the compound did not affect mortality rates. Fluctuating levels of histamine, histaminase, cholinesterase, coproporphyrins and 5-hydroxyindoleacetic acid were attributed to malononitrile administration. Dose-related increased severity of lesions was observed in the liver and spleen. In the liver, congestion became more pronounced with dose, and degeneration and necrosis occurred at 0.50 mg/kg/day. In the

spleen, hemosiderosis and reticulocytosis were observed at 0.25 mg/kg/day and decreased hematopoiesis occurred at 0.50 mg/kg/day. The gastrointestinal tracts of the treated rats were marked by edema and signs of inflammation.

Inhalation exposure of rats to 0.036 mg/ℓ malononitrile vapor for 2 hours/day for 35 days led to signs of irritation during treatment (Panov, 1970). Treated rats showed a slight tendency toward reticulocytosis and, on days 22 and 35, had decreased hemoglobin concentrations, relative to controls. The weight of the lungs, but not the kidney, liver or brain, was increased. Krysiak et al. (1976) gave groups of male Wistar rats 0, 2 or 10 mg/kg/day, and females 0, 2, 10 or 15 mg/kg/day malononitrile by intraperitoneal injection for 6 weeks. For males, dose-related increases in blood urea concentration and liver and adrenal weight were observed. In females, reticulocytosis, erythrocytopenia, increased glucose concentrations and increases in liver and spleen weights were dose-related.

Early clinical use of intravenous doses of malononitrile in psychiatric patients (MacKinnon et al., 1949; Hyden and Hartelius, 1948) was found to be of little or no therapeutic benefit; however, toxic reactions included flushing, tachycardia, headaches, chills and nausea. Acute oral LD_{50}s in rats and mice have ranged from 14-119 mg/kg (Ahmed and Farooqui, 1982; Tanii and Hashimoto, 1985; Krysiak et al., 1976; Panov et al., 1972), and most toxic effects after acute exposure are the same as those seen after cyanide exposure. Szabo et al. (1982), however, observed that high doses of malononitrile exerted neither an ulcerogenic nor an adrenocorticolytic effect, unlike other nitriles. In rats and rabbits given malononitrile parenterally, CNS effects including deposition of polynucleotide and protein substances and necrosis of myelin tissue, were described by Hydin and Hartelius (1948) and Hicks (1950).

6. AQUATIC TOXICITY

6.1. ACUTE

The available data concerning acute toxicity of malononitrile are shown in Table 6-1. The lowest reported acutely toxic concentration was 1.63 mg/ℓ, the 96-hour LC_{50} for rainbow trout, Salmo gairdneri (Abram and Wilson, 1979). The only marine species tested, the mummichog, Fundulus heterochitus, showed a similar sensitivity with a reported LC_{50} of 2.6 mg/ℓ (Pearson, 1975).

6.2. OTHER RELEVANT INFORMATION

Pertinent data regarding chronic toxicity, plant effects and residues of malononitrile in aquatic organisms could not be located in the available literature as cited in the Appendix.

6.3. SUMMARY

The information concerning aquatic toxicity of malononitrile consists of LC_{50} values for two freshwater and one saltwater fish species. All three species, rainbow trout, mosquitofish and mummichog had similar LC_{50} values. The lowest reported acutely toxic concentration was 1.63 mg/ℓ, the 96-hour LC_{50} for rainbow trout (Abram and Wilson, 1979).

TABLE 6-1

Acute Toxicity of Malononitrile to Fishes

Species	Concentration (mg/ℓ)	Effect	Reference
Rainbow trout *Salmo gairdneri*	19.4	12-hour LC_{50}	Abram and Wilson, 1979
	6.22	24-hour LC_{50}	Abram and Wilson, 1979
	4.2	48-hour LC_{50}	Abram and Wilson, 1979
	1.63	96-hour LC_{50}	Abram and Wilson, 1979
Mosquitofish *Gambusia affinis*	>2.6	24-hour LC_{50}	Wolverton et al., 1970
Mummichog *Fundulus heteroclitus*	2.6	72-hour LC_{50}	Pearson, 1975

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

NIOSH (1978) proposed a TWA occupational exposure limit for malononitrile of 3 ppm (~8 mg/m³). Because of the inadequacy of the data base for inhalation exposure to this compound, NIOSH (1978) recommended that a standard be made by analogy of its acute subcutaneous toxicity to that of isobutyronitrile. The standard for isobutyronitrile was based upon its acute toxicity relative to the more adequately studied acetonitrile. Since the minimum lethal inhalation concentration for rats was ~2.4 times as great for acetonitrile as it was for isobutyronitrile, and the standard for acetonitrile was 20 ppm (336 mg/m³); the standard for isobutyronitrile was designated as 8 ppm (22 mg/m³). Furthermore, as the subcutaneous LD_{50} in rats for isobutyroaldehyde was almost 3 times that of malononitrile, NIOSH (1978) recommended the current standard of 3 ppm.

7.2. AQUATIC

Guidelines or standards for the protection of aquatic life from malononitrile could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Pertinent data regarding the carcinogenicity or reproductive effects of malononitrile could not be located in the available literature as cited in the Appendix. Only one study was available on the mutagenicity of malononitrile; the authors reported that the compound did not induce reverse mutations in S. typhimurium TA100 (Rietveld et al., 1983).

Panov et al. (1972) administered, by gastric intubation, 0, 0.25 or 0.50 mg/kg/day malononitrile to male Wistar rats 6 days/week for 120 days. Rats were sacrificed for examination of tissue pathology 2 months after the final treatment. Administration of the compound did not affect mortality rates. Fluctuating levels of histamine, histaminase, cholinesterase, coproporphyrins and 5-hydroxyindoleacetic acid were attributed to malononitrile administration. Dose-related increased severity of lesions was observed in the liver and spleen. In the liver, congestion became more pronounced with dose; degeneration and necrosis occurred at 0.50 mg/kg/day. In the spleen, hemosiderosis and reticulocytosis were observed at 0.25 mg/kg/day, and decreased hematopoiesis occurred at 0.50 mg/kg/day. The gastrointestinal tracts of the treated rats were marked by edema and signs of inflammation.

Inhalation exposure of rats to 0.036 mg/ℓ malononitrile vapor for 2 hours/day for 35 days led to signs of irritation during treatment (Panov, 1970). Treated rats showed a slight tendency toward reticulocytosis and, on days 22 and 35, had decreased hemoglobin concentrations, relative to controls. The weight of the lungs, but not the kidney, liver or brain, was increased. Krysiak et al. (1976) gave groups of male Wistar rats 0, 2 or 10 mg/kg/day, and females 0, 2, 10 or 15 mg/kg/day malononitrile by intraperitoneal injection for 6 weeks. For males, dose-related increases in blood

urea concentration and liver and adrenal weights were observed. In females, reticulocytosis, erythrocytopenia, increased glucose concentrations and increases in liver and spleen sizes were dose-related.

Early clinical use of intravenous doses of malononitrile in psychiatric patients (MacKinnon et al., 1949; Hyden and Hartelius, 1948) was found to be of little or no therapeutic benefit; however, toxic reactions included flushing, tachycardia, headaches, chills and nausea. Acute oral LD_{50}s in rats and mice have ranged from 14-119 mg/kg (Ahmed and Farooqui, 1982; Tanii and Hashimoto, 1985; Krysiak et al., 1976; Panov et al., 1972); most toxic effects after acute exposure are the same as those seen after cyanide exposure. Szabo et al. (1982), however, observed that high doses of malononitrile exerted neither an ulcerogenic nor an adrenocorticolytic effect, unlike other nitriles. In rats and rabbits given malononitrile parenterally, CNS effects including deposition of polynucleotide and protein substances and necrosis of myelin tissue were described by Hydin and Hartelius (1948) and Hicks (1950).

The lack of data regarding the carcinogenic potency of malononitrile warrants derivation of an RfD based upon toxicity findings.

The Panov et al. (1972) 120-day gastric intubation study using rats gives the only available data suitable for risk assessment; however, conclusions from this study are impaired by small sample sizes and the unclear toxicological significance of the biochemical changes found. Moreover, the histological appearance of the livers, spleens and gastrointestinal tracts of controls was not described. Nevertheless, dose-related severity of lesions in the liver and spleen were indicative of genuine toxicity. It seems appropriate to designate the low dose as a LOAEL for subchronic oral toxicity.

A provisional RfD can be calculated after adjusting the low dose of 0.25 mg/kg/day to 0.21 mg/kg/day, because the rats were gavaged 6 times weekly. Using U.S. EPA (1980) guidelines, an uncertainty factor of 10,000 (10 for using a LOAEL instead of a NOAEL, 10 to expand from subchronic to chronic exposure, 10 for interspecies extrapolation and 10 to protect sensitive members of the human population) can be applied to yield an RfD of 2.1×10^{-3} mg/kg/day (0.02 µg/kg/day) or 0.0015 mg/day (1.5 µg/day) for a 70 kg human.

Alternatively, an RfD for malononitrile could be derived by analogy to hydrogen cyanide. The hydrogen cyanide RfD, in turn, was based upon a no-effect level of 10.8 mg/kg/day (U.S. EPA, 1985b) in rats fed a diet fumigated with the compound for 2 years (Howard and Hanzal, 1955). The NOAEL upon which the hydrogen cyanide RfD is based is very close, however, to the rat oral LD_{50} for malononitrile (14 mg/kg) (Krysiak et al., 1976).

The RfD of 0.02 µg/kg/day should be considered provisional until more adequate chronic toxicity and carcinogenicity data become available.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

In the absence of longer-term experimentation, the only studies that can be used to estimate an RQ are the 120-day oral experiment conducted by Panov et al. (1972) and the 35-day inhalation study conducted by Panov (1970). These studies were discussed in Section 5.5. and are summarized in Table 9-1.

RQ rankings based upon the pathological findings of the oral study are provided in Table 9-2. Correction for the 6-day dosing schedule led to adjusted animal doses of 0.21 and 0.43 mg/kg/day. Because the exposure was subchronic, the doses are divided by 10 to approximate chronic exposure. For the low dose, multiplication of the resulting value by the cube root of the ratio of the rat body weight (0.35 kg) to the reference human body weight (70 kg), and further by the reference human body weight results in a chronic human MED of 0.25 mg/day. The MED corresponds to an RV_d of 6.4. Since the pathological effects (hepatic congestion, hemosiderosis and reticulocytosis in the spleen) warrant an RV_e of 5, a CS of 32 results. Calculations at the high dose result in a chronic human MED of 0.51 mg/day and an RV_d of 6.2. Increased hepatocellular necrosis and decreased hematopoiesis warrant an RV_e of 6 for a CS of 35.4. Both of these composite scores correspond to an RQ of 100. Because similar or less severe effects occurred at higher transformed doses in the less than subchronic inhalation study, it is not necessary to calculate a CS for this study.

The effects of hepatocellular necrosis and decreased hematopoiesis observed at the higher dose in the study by Panov et al. (1972) resulted in the higher CS and are recommended as the basis for the RQ (Table 9-3).

TABLE 9-1

Toxicity Summary for Malononitrile[a,b]

Route	Species/ Strain	Sex	No. at Start	Vehicle/ Physical State	Exposure	Transformed Animal Dose (mg/kg/day)	Response	Reference
Oral (gavage)	rat/ Wistar	M	8/group	water	0.25 or 0.50 mg/kg/day, 6 days/week for 120 days	0.21 or 0.43[c]	Varying effects on blood histamine, histaminase, cholinesterase, and urinary 5-hydroxyindoleacetic acid; dose-related increase, then decrease, in urinary coproporphyrins; hepatic necrosis and congestion, and hemosiderosis and reticulocytosis in spleen (which increased in severity with dose) decreased hematopoiesis at high dose; inflammatory effects on gastrointestinal tract	Panov et al., 1972
Inhalation	rat/NR	NR	10	air	36 mg/m³ 2 hours/day for 35 days	1.9[d]	Hyperthermia, reticulocytosis, decreased hemoglobin concentration, increased lung weight	Panov, 1970

[a]Average weight of rats was 0.35 kg [reference body weight (U.S. EPA, 1980)].

[b]Purity of compound was not reported

[c]Calculated by expanding the dose over 7 days

[d]Calculated by multiplying the exposure concentration by 2 hours/24 hours by the rat inhalation rate (0.223 m³/day) and dividing by the reference rat body weight (U.S. EPA, 1980)

NR = Not reported

TABLE 9-2

Oral Composite Scores for Malononitrile in the Rat[a,b]

Animal Dose (mg/kg/day)	Chronic Human MED[c] (mg/day)	RV_d	Effect	RV_e	CS	RQ
0.21	0.25	6.4	Hepatic congestion; hemolysis; hemosiderin deposition	5	32	100
0.43	0.51	5.9	Hepatic congestion; hepatocellular necrosis; depletion of red and white blood cells from the red pulp; decreased hematopoiesis	6	35.4	100

[a]Source: Panov et al.,1972

[b]Administered by gavage

[c]The doses were divided by an uncertainty factor of 10 to approximate chronic exposure.

TABLE 9-3

MALONONITRILE

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral (gavage)
Dose*:	0.51 mg/day
Effect:	hepatocellular necrosis, reduced hematopoiesis
Reference:	Panov et al., 1972
RV_d:	5.9
RV_e:	6
Composite Score:	35.4
RQ:	100

*Equivalent human dose

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Pertinent data regarding the carcinogenicity of malononitrile were not located and this chemical is not scheduled for testing by the National Toxicology Program (NTP, 1986). Malononitrile was found not to be mutagenic for S. typhimurium strain TA100, with or without metabolic S-9 activation (Rietvald et al., 1983). In the absence of available carcinogenicity data, a potency factor for malononitrile cannot be calculated. Based on U.S. EPA (1984) guidelines for carcinogen risk assessment and unavailability of human data, the overall weight of evidence classification is Group D, meaning malononitrile cannot be classified as a human carcinogen and cannot be ranked further in the CERCLA Hazard Ranking Scheme for Reportable Quantities.

10. REFERENCES

Abram, F.S.H. and P. Wilson. 1979. The acute toxicity of CS to rainbow trout. Water Res. 13(7): 631-635.

Ahmed, A.E. and M.Y.H. Farooqui. 1982. Comparative toxicities of aliphatic nitriles. Toxicol. Lett (Amst). 12(2-3): 157-164.

Aldrich Chemical Co. 1986. Catalog Handbook of Fine Chemicals. Aldrich Chemical Co., Inc., Milwaukee, WI. p. 837.

Block, S., F. Raulin, G. Toupance and R. Buvet. 1973. Decomposition of malononitrile in aqueous alkaline solution. C.R. Acad. Sci. Ser. C. 276(11): 915-18. (Fre.) (CA 78:146988k)

Castro, C.E., R.S. Wade and N.O. Belser. 1978. Conversion of oxyhemoglobin to methemoglobin by organic and inorganic reductants. Biochemistry. 17(2): 225-231.

Frankenberg, L. and B. Sorbo. 1973. Formation of cyanide from o-chlorobenzylidene malononitrile and its toxicological significance. Arch. Toxikol. 31(2): 99-108.

Gutsche, C.D. and D.J. Pasto. 1975. Fundamentals of Organic Chemistry. Prentice-Hall, Inc., Englewood Cliffs, NJ. p. 428.

Hawley, G.G. 1981. The Condensed Chemical Dictionary, 10th ed. Van Nostrand Reinhold Co., New York, NY. p. 639.

Hicks, S.P. 1950. Brain metabolism *in vivo*--II. The distribution of lesions caused by azide malononitrile, plasmocid and dinitrophenol poisoning in rats. Arch. Pathol. 50: 5545-561.

Hoecker, J.E., P.R. Durkin, A. Hanchelt, L. Davis, W.M. Meylan and S.J. Bosch. 1977. Information Profiles on Potential Occupational Hazards. Prepared by Syracuse Research Corp., Syracuse, NY under Contract No. 210-77-0120. National Institute for Occupational Safety and Health, Rockville, MD.

Howard, J.W. and R.F. Hanzal. 1955. Chronic toxicity for rats of food treated with hydrogen cyanide. Agric. Food Chem. 3: 325-329.

Hyden, H. and H. Hartelius. 1948. Stimulation of the nucleoprotein-production in the nerve cells by malononitrile and its effect on psyelic function in mental disorders. Acta. Psychiat. Neurol. 48: 1-117.

Jenks, W.R. 1979. Cyanides. *In*: Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 7, M. Grayson and D. Eckroth, Ed. John Wiley and Sons Inc., New York. p. 309.

Jones, G.R. and M.S. Israel. 1970. Mechanism of toxicity of injected CS gas. Nature. 228: 1315-1316.

Krysiak, B., T. Czajkowska and J. Stetkiewicz. 1976. Acute and subacute toxic action of malononitrile. Med. Pr. 27(1): 1-19.

Lyman, W.J., W.F. Reehl and D.H. Rosenblatt. 1982. Handbook of Chemical Property Estimation Methods. Environmental Behavior of Organic Compounds. McGraw-Hill Book Co., New York, NY. p. 14-18.

MacKinnon, I.H., P.H. Hock, L. Cammer and H.B. Waelsch. 1949. The use of malononitrile in the treatment of mental illnesses. Am. J. Psychiatry. 105: 686-688.

Marion, C.V. and G.W. Malaney. 1963. The oxidation of aliphatic compounds by Alcalegenes faecalis. J. Water Pollut. Control Fed. 35: 1269-1284.

Mendelson, J., J.H. Mendelson, B.J. Fox and R.G. Grenell. 1954. Stability and absorption spectrum of malononitrile. Science. 120: 266-269.

NIOSH (National Institute for Occupational Safety and Health). 1978. Criteria for a Recommended Standard...Occupational Exposure to Nitriles. U.S. DHEW, PHS, CDC, Rockville, MD.

NTP (National Toxicology Program). 1986. Management Status Report. 3/12/86.

Panov, I.K. 1969. Study of acute dicyanomethane toxicity in animals. J. Eur. Toxicol. 2: 292-299. (Fre.) (Cited in NIOSH, 1978)

Panov, I.K. 1970. Toxicological study of dicyanomethane. J. Eur. Toxicol. 3: 58-63. (Fre.)

Panov, I., M. Zlateva and G. Antov. 1972. Toxicological characteristics of dicyanomethane. Chronic effects in white rats. Khig. Zdraveopazvane. 15(6): 553-562. (In Bulgarian with English translation)

Pearson, J.G. 1975. The toxicity of the riot control agent CS (o-chlorobenzylidene malononitrile) and its hydrolysis products to the mummichog, Fundulus heteroclitus. Edgewood Arsenal, Aberdeen Proving Ground, MD. 800: 24. (Cited in SPHERE, 1985)

Rietveld, E.C., L.P.C. Delbressine, T.H.J. Waegemaekers and F. Seutter-Berlage. 1983. 2-Chlorobenzylmercapturic acid, a metabolite of the riot control agent 2-chlorobenzylidene malononitrile (CS) in the rat. Arch. Toxicol. 54(2): 139-144.

Sax, N.I., Ed. 1985. Dangerous Properties of Industrial Materials, 6th ed. Van Nostrand Reinhold Co., New York. p. 1727-1728.

SPHERE (Scientific Parameters for Health and the Environment, Retrieval and Estimation). 1985. October, 1985: On-line. U.S. EPA, Office of Toxic Substances, Washington, DC.

SRI (Stanford Research Institute). 1985. 1985 Directory of Chemical Producers. United States of America. SRI International, Menlo Park, CA. p. 674.

Stern, J., H. Weil-Malherbe and R.H. Green. 1952. The effects and the fate of malononitrile and related compounds in animal tissues. Biochem. J. 52: 114-125.

Szabo, S., E.S. Reynolds and S.H. Unger. 1982. Structure-activity relations between alkyl nucleophilic chemicals causing duodenal ulcer and adrenocortical necrosis. J. Pharmacol. Exp. Ther. 223(1): 68-76.

Tanii, H. and K. Hashimoto. 1985. Structure-acute toxicity relationship of dinitriles in mice. Arch. Toxicol. 57(2): 88-93.

U.S. EPA. 1977. Computer print-out of non-confidential production data from TSCA inventory. OPTS, CID, U.S. EPA, Washington, DC.

U.S. EPA. 1980. Guidelines and Methodology used in the Preparation of Health Effects Assessment Chapters of the Ambient Water Quality Criteria Documents. ECAO, OHEA, ORD, U.S. EPA, Cincinnati, OH. [Also published in Federal Register, 45(231): 79347-79357]

U.S. EPA. 1984. Proposed Guidelines for Carcinogen Risk Assessment. Federal Register. 49(227): 46296-46301.

U.S. EPA. 1985a. Health and Environmental Effects Profile on Acetonitrile. Environmental Criteria and Assessment Office, U.S. EPA, Cincinnati, OH. ECAO-CIN-P137. Final Draft.

U.S. EPA. 1985b. Drinking Water Criteria Document for Cyanide. ECAO, Cincinnati, OH. ECAO/CIN-442. Final Draft.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 3rd ed. Van Nostrand Reinhold Co., New York, NY. p. 805.

Willhite, C.C. and R.P. Smith. 1981. The role of cyanide liberation in the acute toxicity of alphatic nitriles. Toxicol. Appl. Pharmacol. 59(3): 589-602.

Windholz, M., Ed. 1983. The Merck Index. An Enyclopedia of Chemicals, Drugs and Biologicals, 10th ed. Merck and Co., Inc. Rahway, NJ. p. 815.

Wolverton, B.C., D.D. Harris and R.C. Voight. 1970. Toxicity of CS-2-Decontamination Products. Tech. Report AFATL-TR-70-68, Air Force Armament Labs. NTIS AD-879. (Cited in SPHERE, 1985)

APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN International
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in October, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1985. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1985-1986. Cincinnati, OH. 114 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., Littleton, MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1986. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, N.I. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1984. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1985. Status Report on Rebuttable Presumption Against Registration (RPAR) or Special Review Process. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

U.S. EPA. 1985. CSB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422, Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.